Palladium-Catalyzed Zinc-Amide-Mediated C[BOND]H Arylation of Fluoroarenes and Heteroarenes with Aryl Sulfides.

AUTHOR(S):

Otsuka, Shinya; Yorimitsu, Hideki; Osuka, Atsuhiro

CITATION:

Otsuka, Shinya ...[et al]. Palladium-Catalyzed Zinc-Amide-Mediated C[BOND]H Arylation of Fluoroarenes and Heteroarenes with Aryl Sulfides.. Chemistry - A European Journal 2015, 21(42): 14703-14707

ISSUE DATE:

2015-10-12

URL:

http://hdl.handle.net/2433/203038

Palladium-catalyzed Zinc-amide-mediated C–H Arylation of Fluoroarenes and Heteroarenes with Aryl Sulfides

Shinya Otsuka,[a] Hideki Yorimitsu,*[a,b] and Atsuhiro Osuka[a]

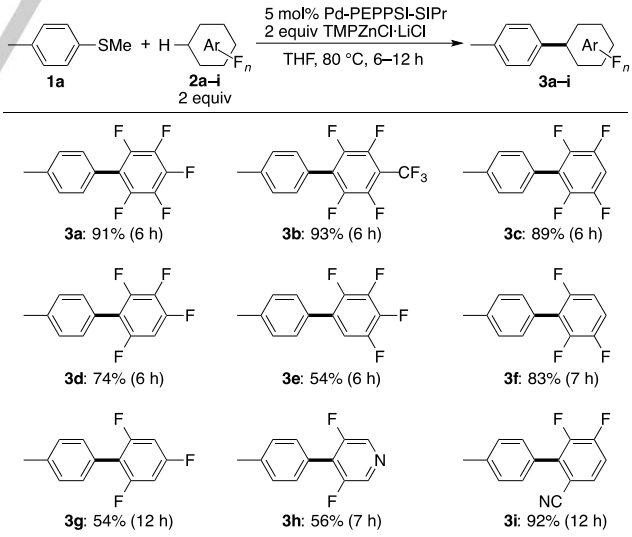
Dedication ((optional))

Abstract: C–H arylation of polyfluoroarenes and heteroarenes with aryl sulfides proceeds smoothly with the aid of a palladium-N-heterocyclic carbene catalyst. A bulky zinc amide, TMPZnCl·LiCl, plays a key role as an effective base to generate the corresponding arylzinc species in situ. This arylation is practically much easier to perform than our previous method that necessitates preparation of arylzinc reagents in advance from the corresponding aryl halides. Aryl sulfides that are prepared through sulfur-specific reactions such as S_NAr sulfanylation and extended Pummerer reactions undergo this direct arylation, which offers interesting transformations that are otherwise difficult to achieve with the conventional halogen-based organic synthesis.

Organosulfur compounds have played unique roles in organic chemistry owing to their intriguing reactivities, biological activities, or physical properties.[1] Among them, aryl sulfides occupy an important position, and new methods for the synthesis of aryl sulfides have hence been actively developed.[2] In contrast, development of new reactions of aryl sulfides has been reported only scatteringly. Transition-metal-catalyzed cross-coupling reactions of aryl sulfides[3] are difficult to achieve because sulfur species strongly poison catalysts and C(sp^2)–S bonds are rather strong to cleave. One can overcome these difficulties when Grignard reagents are employed as nucleophiles[4] or aryl sulfides have special structures that facilitate efficient conversions.[5–7] We are interested in catalytic transformations of organosulfur compounds[4e–g,8] and recently developed general cross-coupling reactions of aryl sulfides with arylzinc reagents, using a palladium-NHC complex as a catalyst.[8b] Although our Negishi-type cross-coupling shows wide scope and proceeds under mild conditions, the reactions necessitate preparation of the arylzinc reagents from the corresponding haloarenes in advance.

Transition-metal-catalyzed direct C–H arylation of arenes with aryl halides has emerged as a promising alternative to the conventional cross-coupling.[9] However, due to the aforementioned difficulties in catalytically transforming aryl sulfides, it is just a few months ago that Wang admirably reported the first example of direct C–H arylation with aryl sulfides, wherein a palladium-diphosphine catalyst and sodium *t*-butoxide were employed.[10] Nevertheless, the arylation lacks generality: electron-neutral and -rich aryl sulfides reacted moderately even at 140 ˚C and only oxazole derivatives smoothly underwent the arylation. To expand the utility of aryl sulfides, here we report efficient and general conditions for C–H arylation of polyfluoroarenes[11,12] and heteroarenes[13] with aryl sulfides.

We chose the reaction of methyl *p*-tolyl sulfide (**1a**) with pentafluorobenzene (**2a**) as a model reaction. We screened palladium catalysts and bases (see the Supporting Information for optimization) to find that Pd-PEPPSI-SIPr[14] and 2,2,6,6-tetramethylpiperidylzinc chloride·lithium chloride complex[15,16] (TMPZnCl·LiCl) are the best catalyst/base combination to afford **3a** in 91% yield (Scheme 1). As we found previously,[8] Pd-PEPPSI-SIPr, a palladium NHC complex, is again the key for the success. TMPZnCl·LiCl is known as an exquisite base for deprotonative zincation of electron-deficient or heteroarenes, tolerating various functional groups.[15] We are delighted to find that TMPZnCl·LiCl serves to generate pentafluorophenylzinc species in situ[17] compatibly with successive Negishi-type cross-coupling, which allowed us to achieve C–H arylation under mild conditions. Another advantage of using the zinc base is that the resulting zinc methylthiolate species is not nucleophilic enough to induce conceivable S_NAr displacement of a fluoro group with a methylsulfanyl group.[18]



Scheme 1. Scope of Polyfluoroarenes.

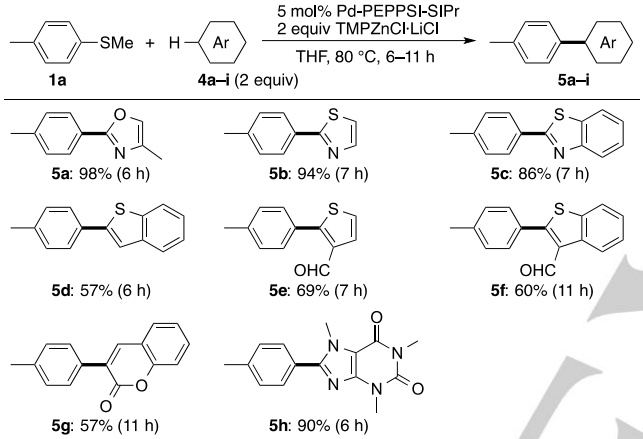
A variety of polyfluoroarenes can be used for this reaction. Perfluorinated 2,3,5,6-tetrafluorobenzotrifluoride (**2b**) reacted smoothly to afford **3b** in excellent yield. For the less fluorinated arenes, the efficiency of arylation is likely to depend heavily on the acidity of the proton that is deprotonated: the reactions of

[a] S. Otsuka, Prof. Dr. H. Yorimitsu, Prof. Dr. A. Osuka
Department of Chemistry, Graduate School of Science
Kyoto University
Sakyo-ku, Kyoto 606-8502 (Japan)
E-mail: yori@kuchem.kyoto-u.ac.jp
[b] Prof. Dr. H. Yorimitsu
ACT-C, JST
Sakyo-ku, Kyoto 606-8502 (Japan)

Supporting information for this article is given via a link at the end of the document.

1,2,4,5-tetrafluoro-, 1,2,3,5-tetrafluoro, and 1,2,4-trifluorobenzene gave the corresponding products **3c**, **3d**, and **3f** in high yields whereas less acidic 1,2,3,4-tetrafluoro- and 1,3,5-trifluorobenzene were converted less efficiently to **3e** and **3g**, respectively.[19] The arylation of **2f** took place regioselectively at the 4 position under the acidity control. 3,5-Difluoropyridine (**2h**) proved to be acidic enough to be arylated at the 4 position. A cyano group is also effectively electron-withdrawing to yield **3j** in excellent yield with exclusive regioselectivity.

Not only polyfluoroarenes but also five-membered heteroarenes reacted under the reaction conditions (Scheme 2). Compared with Wang's procedure, 4-methyloxazole, thiazole, benzothiazole reacted much more smoothly to give 2-arylated products **5a–c** in high yields with exclusive regioselectivity. Besides azoles, thiophene derivatives reacted at the 2 position to yield **5d–f** in good yields. Six-membered coumarin and bioactive caffeine also gave the desired products **5g** and **5h**, respectively.

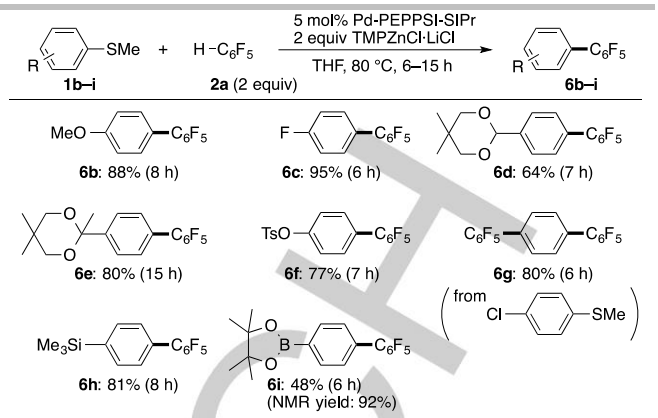


Scheme 2. Scope of Heteroarenes.

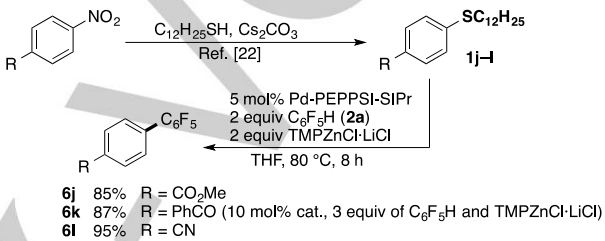
The scope of aryl sulfides is also broad (Scheme 3). Neither electron-donating methoxy group nor electron-withdrawing fluoro group retarded the reaction (**6b** and **6c**). Acetal-protected aldehyde and ketone were compatible (**6d** and **6e**). A tosyloxy group, which can be a leaving group of cross-coupling,[8b,20] was tolerated to yield **6f** although 4-chlorothioanisole underwent twofold arylation to give terphenyl **6g**. Interestingly, trimethylsilyl group and pinacolatoboryl group survived under the basic conditions (**6h** and **6i**[21]).

When combined with reactions that are unique to organosulfur compounds, this direct arylation offers interesting transformations that are otherwise difficult to achieve.

Aryl sulfides **1j–l** bearing a carbonyl or cyano group were synthesized via nucleophilic aromatic substitution of electron-deficient nitroarenes with dodecanethiol (Scheme 4).[22] These aryl sulfides underwent catalytic pentafluorophenylation selectively at the dodecylsulfanyl unit with the polar functional groups untouched. The overall two-step transformation represents displacement of a nitro group with a perfluoroaryl group by using a unique reactivity of organosulfur species.

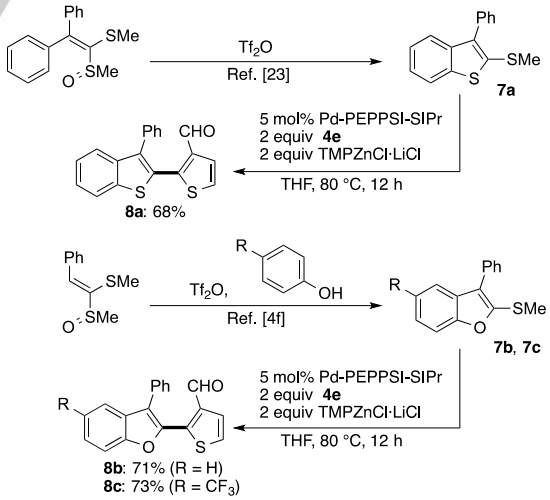


Scheme 3. Scope of Aryl Sulfides.



Scheme 4. S_NAr Displacement of NO_2 Group Followed by C–H Arylation.

Our group reported the concise synthesis of multi-substituted benzothiophenes[23] and benzofurans[4f,24] containing a methylsulfanyl group through extended Pummerer chemistry of ketene dithioacetal monoxides[25] (Scheme 5). We found that compounds **7** thus synthesized are good substrates for the direct arylation with thiophene-3-carbaldehyde (**4e**) in spite of the steric hindrance of the neighboring phenyl group.

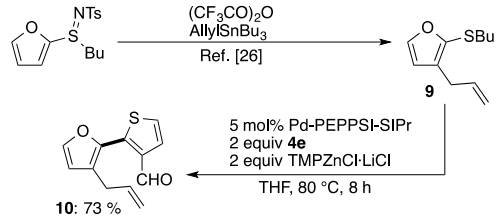


Scheme 5. Synthesis of 2,3-Diarylbenzothiophene and Benzofuran.

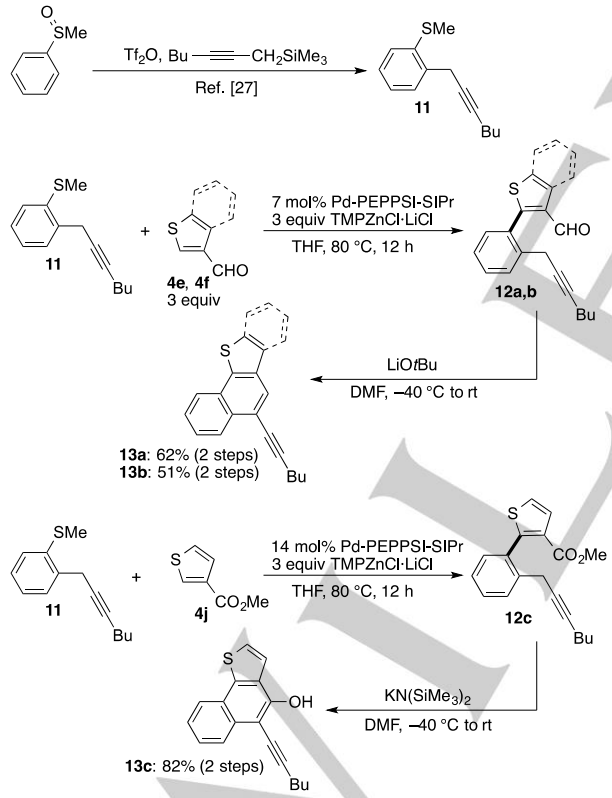
Padwa developed 3-allylation of 2-heteroaryl sulfilylimines under Pummerer-type conditions.[26] According to this protocol, we synthesized 2-butylsulfanyl-3-allylfuran (**9**), which was then

subjected to the arylation conditions to yield the corresponding 3-allyl-2-thienylfuran **10** (Scheme 6).

Procter reported extended Pummerer reactions of aryl sulfoxides with propargylsilanes to provide 2-propargylaryl sulfides.[27] We found that such a 2-propargylated product **11** is a useful precursor of naphthothiophene derivatives (Scheme 7). Arylation of thiophene derivatives **4e**, **4f**, and **4j** bearing a carbonyl group at the 3 position with **11** proceeded smoothly despite steric repulsion. We were glad to find that treatment of **12a** and **12b** with LiO*t*Bu led to dehydration to yield alkynylated naphthothiophene **13a** and benzonaphthothiophene **13b**, respectively. Similarly, treatment of **12c** with $KN(SiMe_3)_2$ resulted in condensation followed by tautomerization to yield hydroxynaphthothiophene **13c** in high yield.



Scheme 6. 3-Allylation Followed by 2-Arylation.



Scheme 7. Arylation of 3-Carbonylthiophene Derivatives with 2-Propargylphenyl Sulfide Followed by Condensation.

In summary, we have developed an efficient protocol for direct arylation of polyfluoroarenes and heteroarenes with aryl sulfides. Our system is broad in scope and exhibits intriguing orthogonal reactivity, leaving the tosyloxy, trimethylsilyl, and pinacolatoboryl groups intact. This arylation can follow S_NAr displacement of a nitro group with an alkylsulfanyl group or extended Pummerer reactions, which provides new transformations by taking advantage of the unique reactivities of organosulfur compounds. Our current studies are directed to disseminate C–S-based organic synthesis that complements C–X-based synthesis.

Experimental Section

The reaction of methyl *p*-tolyl sulfide (**1a**) and pentafluorobenzene (**2a**) is representative (Scheme 1, **3a**). Pd-PEPPSI-SIPr (17.0 mg, 0.025 mmol) was placed in a 20-mL Schlenk tube under nitrogen. After additions of TMPZnCl·LiCl (1.0 mL, 1.0 mmol, 1.0 M in THF), pentafluorobenzene (168.1 mg, 1.0 mmol), methyl *p*-tolyl sulfide (69.1 mg, 0.50 mmol), and THF (1.0 mL), the resulting mixture was heated to 80 °C and stirred for 6 h at the same temperature. After being cooled to 20 °C, the reaction was quenched with saturated $NaHCO_3$ aq. (20 mL). Organic compounds were extracted with *n*-hexane (10 mL×3). The combined organic layer was passed through pads of anhydrous sodium sulfate and activated alumina, and concentrated in vacuo. Purification by chromatography on silica gel (*n*-hexane) provided **3a** (117.1 mg, 0.45 mmol, 91%).

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research from MEXT (No.: 25107002 “Science of Atomic Layers”) and from JSPS (Nos.: 24685007 (Young Scientists (A)) and 26620081 (Exploratory Research)). H.Y. thanks Japan Association for Chemical Innovation for financial support.

Keywords: C–H arylation • C–S bond activation • organosulfur compounds • palladium • organozinc compounds

[1] a) E. Block, *Advances in Sulfur Chemistry*, JAI Press, Greenwich, **1994**; b) R. J. Cremlyn, *An Introduction of Organosulfur Chemistry*, Wiley, Chichester, **1996**; c) *Organic Sulfur Chemistry: Biochemical Aspects* (Eds.: S. Oae and T. Okuyama), CRC Press, Boca Raton, **1992**; d) *Organic Sulfur Chemistry: Structure and Mechanism* (Ed.: S. Oae), CRC Press, Boca Raton, **1991**.

[2] a) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205; b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; *Angew. Chem.* **2003**, *115*, 5558; c) C. C. Eichman, J. P. Stambuli, *Molecules* **2011**, *16*, 590; d) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596; e) H. Liu, X. Jiang, *Chem. Asian J.* **2013**, *8*, 2546; f) C.-F. Lee, Y.-C. Liu, S. S. Badsara, *Chem. Asian J.* **2014**, *9*, 706; g) J. L. Farmer, M. Pompeo, A. J. Lough, M. G. Organ, *Chem. Eur. J.* **2014**, *20*, 15790 and references cited therein.

[3] a) T.-Y. Luh, Z.-J. Ni, *Synthesis* **1990**, 89; b) S. R. Dubbaka, P. Vogel, *Angew. Chem. Int. Ed.* **2005**, *44*, 7674; *Angew. Chem.* **2005**, *117*, 7848; c) H. Prokopcová, C. O. Kappe, *Angew. Chem. Int. Ed.* **2008**, *47*, 3674; *Angew. Chem.* **2008**, *120*, 3732; d) E. C. Garnier-Amblard, L. S. Liebeskind, *Boronic Acids, 2nd Ed.* (Ed: D. G. Hall), Wiley, Weinheim, **2011**, Chapter 7; e) L. Wang, W. He, Z. Yu, *Chem. Soc. Rev.* **2013**, *42*, 599; f) S. G. Modha, V. P. Mehta, E. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 5042; g) F. Pan, Z.-J. Shi, *ACS Catal.* **2014**, *4*, 280.

[4] Recent examples for cross-coupling reaction of aryl sulfides with Grignard reagents: a) V. P. Mehta, S. G. Modha, E. Van der Eycken, *J. Org. Chem.* **2009**, *74*, 6870; b) J. Ma, L. Peng, X. Zhang, Z. Zhang, M. Campbell, J. Wang, *Chem. Asian J.* **2010**, *5*, 2214; c) L. Hintermann, M. Schmitz, Y. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2411; d) A. J. Eberhart, J. E. Imbriglio, D. J. Procter, *Org. Lett.* **2011**, *13*, 5882; e) S. Kanemura, A. Kondoh, H. Yorimitsu, K. Oshima, *Synthesis* **2008**, 2659; f) K. Murakami, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2014**, *53*,

7510; *Angew. Chem.* **2014**, *126*, 7640; g) A. Baralle, S. Otsuka, V. Guérin, K. Murakami, H. Yorimitsu, A. Osuka, *Synlett* **2015**, *26*, 327.

[5] Cross-coupling reaction of aryl sulfides with a special sulfur leaving group: a) J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376; b) J. Srogl, W. Liu, D. Marshall, L. S. Liebeskind, *J. Am. Chem. Soc.* **1999**, *121*, 9449; c) L. S. Liebeskind, J. Srogl, C. Savarin, C. Polanco, *Pure Appl. Chem.* **2002**, *74*, 115.

[6] Very selected examples of cross-coupling reactions of reactive azaaryl sulfides: a) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979; b) M. Egi, L. S. Liebeskind, *Org. Lett.* **2003**, *5*, 801; c) F.-A. Alphonse, F. Suzenet, A. Keromnes, B. Lebret, G. Guillaumet, *Org. Lett.* **2003**, *5*, 803; d) K. Lee, C. M. Counceller, J. P. Stambuli, *Org. Lett.* **2009**, *11*, 1457; e) J.-M. Begouin, M. Rivard, C. Gosmini, *Chem. Commun.* **2010**, *46*, 5972; f) L. Melzig, A. Metzger, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 2948; g) S. G. Modha, J. C. Trivedi, V. P. Mehta, D. S. Ermolat'ev, E. Van der Eycken, *J. Org. Chem.* **2011**, *76*, 846; h) M. Koley, L. Wimmer, M. Schnürch, M. D. Mihovilovic, *Eur. J. Org. Chem.* **2011**, 1972; i) S. Dahbi, P. Bisseret, *Eur. J. Org. Chem.* **2012**, 3759.

[7] Cross-coupling reactions of aryl sulfides bearing a directing group: a) J. F. Hooper, R. D. Young, I. Pernik, A. S. Weller, M. C. Willis, *Chem. Sci.* **2013**, *4*, 1568; b) F. Pan, H. Wang, P.-X. Shen, J. Zhao, Z.-J. Shi, *Chem. Sci.* **2013**, *4*, 1573; c) G. S. Creech, O. Kwon, *Chem. Sci.* **2013**, *4*, 2670; d) J.-X. Liu, Y.-J. Liu, W.-T. Du, Y. Dong, J. Liu, M. Wang, *J. Org. Chem.* **2013**, *78*, 7293.

[8] a) Y. Ookubo, A. Wakamiya, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2012**, *18*, 12690; b) S. Otsuka, D. Fujino, K. Murakami, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2014**, *20*, 13146.

[9] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; c) L. C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichim. Acta* **2007**, *40*, 35; d) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; e) L. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; f) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013; g) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; h) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087; i) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; j) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *Angew. Chem.* **2009**, *121*, 9976; k) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; l) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; m) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; n) A. Lei, W. Liu, C. Liu, M. Chen, *Dalton Trans.* **2010**, *39*, 10352; o) K. Hirano, M. Miura, *Synlett* **2011**, 294; p) C. Liu, H. Zhang, W. Sui, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; q) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; (r) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; (s) C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584; t) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; u) H. Yorimitsu, A. Osuka, *Asian J. Org. Chem.* **2013**, *2*, 356; v) F. Shibahara, T. Murai, *Asian J. Org. Chem.* **2013**, *2*, 624; w) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; x) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17; y) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2014**, *6*, 1824; z) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906; aa) R. Rossi, F. Bellina, M. Lessi, C. Manzini, L. A. Perego, *Synthesis* **2014**, *46*, 2833; bb) K. Hirano, M. Miura, *Top. Catal.* **2014**, *57*, 878; cc) M. Miura, T. Satoh, K. Hirano, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 751; dd) Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66; *Angew. Chem.* **2015**, *127*, 68.

[10] F. Zhu, Z.-X. Wang, *Org. Lett.* **2015**, *17*, 1601.

[11] Reviews on the importance of polyfluoroarenes: a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119.

[12] Catalytic C–H arylation of polyfluoroarenes with aryl electrophiles: a) N. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754; b) J. W. W. Chang, E. Y. Chia, C. L. L. Chai, J. Seayad, *Org. Biomol. Chem.* **2012**, *10*, 2289; c) X. Zhu, F. Li, W. Su, *Tetrahedron Lett.* **2013**, *54*, 1285; d) M. Lesieur, F. Lazreg, C. S. J. Cazin, *Chem. Commun.* **2014**, *50*, 8927; e) H.-H. Zhang, J. Dong, Q.-S. Hu, *Eur. J. Org. Chem.* **2014**, 1327; Oxidative C–H arylation of polyfluoroarenes with arenes: f) Y. Wei, J. Kan, M. Wang, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 3346; g) Y. Wei, W. Su, *J. Am. Chem. Soc.* **2010**, *132*, 16377; h) T. Miao, L. Wang, *Adv. Synth. Catal.* **2014**, *356*, 429.

[13] Very selected recent examples of C–H arylation of heteroarenes: a) S. Tani, T. Uehara, J. Yamaguchi, K. Itami, *Chem. Sci.* **2014**, *5*, 123; b) N. A. Strotman, H. R. Chobanian, Y. Guo, J. He, J. E. Wilson, *Org. Lett.* **2010**, *12*, 3578; c) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404; d) F. Bellina, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2006**, 1379; e) H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449.

[14] a) M. G. Organ, M. Abdel-Hade, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150; b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Aldrichim. Acta* **2006**, *39*, 97; c) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180; d) M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* **2008**, 2776.

[15] a) M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837; b) T. Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 1914; *Angew. Chem.* **2011**, *123*, 1954; c) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584; d) A. Unsinn, M. J. Ford, P. Knochel, *Org. Lett.* **2013**, *15*, 1128.

[16] Review for deprotonative metalation: a) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.* **2007**, *46*, 3802; *Angew. Chem.* **2007**, *119*, 3876; References for other TMPZn bases: b) Y. Kondo, M. Shilai, M. Uchiyama, T. Sakamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3539; c) T. Imahori, M. Uchiyama, T. Sakamoto, U. Kondo, *Chem. Commun.* **2001**, 2450; d) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo. *J. Am. Chem. Soc.* **2002**, *124*, 8514; e) M. Uchiyama, Y. Matsumoto, D. Nobuto, T. Furuyama, K. Yamaguchi, K. Morokuma, *J. Am. Chem. Soc.* **2006**, *128*, 8748; f) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; *Angew. Chem.* **2007**, *119*, 7829; g) S. Wunderlich, P. Knochel, *Org. Lett.* **2008**, *10*, 4705; h) S. Wunderlich, P. Knochel, *Chem. Commun.* **2008**, 6387; i) M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1468.

[17] We confirmed that deprotonation to form arylzinc species is faster than the successive arylation. See supporting information for details.

[18] MeSNa reacted with **3a** smoothly to give a substituted product. See supporting information for details.

[19] For the acidity of arenes, see: K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568.

[20] a) Z.-Y. Tang, Q.-S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058; b) B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954.

[21] The moderate isolated yield of **6i** is due to the instability of **6i** during silica gel column purification. For similar difficulty in purification on silica gel, see: S. Hitosugi, D. Tanimoto, W. Nakanishi, H. Isobe, *Chem. Lett.* **2012**, *41*, 972.

[22] A. Kondoh, H. Yorimitsu, K. Oshima, *Tetrahedron* **2006**, *62*, 2357.

[23] S. Yoshida, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 26, 5573.

[24] T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2010**, *132*, 34, 11838.

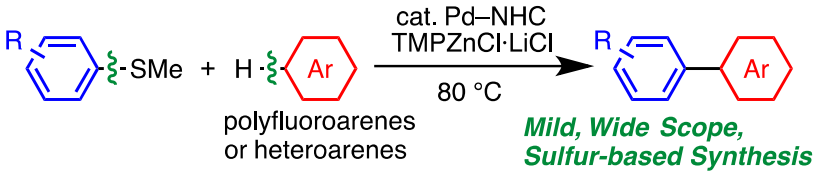
[25] a) K. Murakami, H. Yorimitsu, A. Osuka, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1193; b) K. Murakami, H. Yorimitsu, A. Osuka, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 441; c) H. Yorimitsu, *J. Synth. Org. Chem., Jpn.* **2013**, *71*, 341.

[26] A. Padwa, S. Nara, Q. Wang, *Tetrahedron Lett.* **2006**, *47*, 595.

[27] a) A. J. Eberhart, D. J. Procter, *Angew. Chem. Int. Ed.* **2014**, *52*, 4008; *Angew. Chem.* **2014**, *125*, 4100; b) A. J. Eberhart, H. J. Shrives, E. Álvarez, A. Carrër, Y. Zhang, D. J. Procter, *Chem. Eur. J.* **2015**, *21*, 7428.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



Efficient C–H arylation of polyfluoroarenes and heteroarenes with aryl sulfides proceeds with the aid of a palladium-NHC catalyst and a bulky zinc amide base to generate the corresponding arylzinc species in situ. Aryl sulfides that are prepared through sulfur-specific reactions such as S_NAr sulfanylation and extended Pummerer reactions undergo this direct arylation, which offers interesting transformations that are otherwise difficult to achieve with the conventional halogen-based organic synthesis.

S. Otsuka, Prof. Dr. H. Yorimitsu, Prof. Dr. A. Osuka*

Page No. – Page No.

Palladium-catalyzed Zinc-amide-mediated C–H Arylation of Fluoroarenes and Heteroarenes with Aryl Sulfides